REMARKS

Claims 1, 4-5, 7-9, 11-16 and 18-29 are pending. Claims 18-28 have been withdrawn from consideration; claims 2, 3, 6, 10, and 17, as well as claim 30, have been canceled without prejudice or disclaimer; and claims 1, 4-5, 7-9, 11-16, and 29 are currently under active examination.

Claims 1 and 29 are amended herein. The amendments raise no issues of new matter. Claim 1 is amended to delete reference to the term "about"; while claim 29 is amended to recite the definite article "The".

Claim 1 also is amended to specify that the carrier protein is covalently coupled to the polysaccharide "through cleaved sialic acid exocyclic side chains of the polysaccharide fragments." Support for this amendments can be found in the specification, e.g., at paragraphs [0052]-[0053], describing that aldehyde groups are selectively introduced into the sialic acid exocyclic side chain of the polysaccharide, and Figure 1. As can be seen from Figure 1, hyrdoxyl groups can be present on carbons 7, 8 and 9 of the scialic acid residues which upon oxidation results in aldehyde groups on carbons 7 or 8, although according to the Applicants it is believed aldehyde groups favor formation on carbon 8. The specification further describes the formation of amine bonds between amino groups of proteins and the adehyde groups of the oxidized polysaccharides through reductive amination.

Claim 1 is further amended to specify that the de-O-acetylation is carried out "by base hydrolysis," support for which can be found throughout the specification, e.g., at paragraphs [0028]-[0034].

The element in the claims that the conjugate is completely N-acetylated is supported at paragraph [0039] that recites the re-N-acetylation step "ensures that all free primary amino groups that may have been generated during the base hydrolysis are re-N-actylated." Further support may be found at paragraph [0093] that reports the percent of O-acetylation relative to the N-acetyl groups of the sialic acid groups per repeat unit, where the specification states there are 0.6 M of O-acetyl groups per repeating unit "(or 60% relative to the N-acetyl group of sialic acid) equally distributed between the C7 and C9 position of their scialic acids." The equivalence of the 0.6 M per repeat unit with the 60% of scialic acids implies that each repeat unit has a corresponding N-acetyl group, thus supporting the element that the polysaccharides are completely N-acetylated.

Accordingly, the amendments introduce no new matter.

Withdrawn Rejections

Applicants acknowledge withdrawal of previous rejection of claims 1, 4-5, 7-9, 11-16, and 29-30 under 35 U.S.C. 103(a), in view of Costantino WO 03/007985 and Porro U.S. 2006/0165730, and further in view of Michon et al. WO 00/10599. Action at page 2. The Examiner notes, however, that the rejection may be reinstated depending on the resolution of the alleged new matter issues raised by Applicants' prior claim amendments. Id.

New Rejections under 35 U.S.C. 112, 1st paragraph

The Office rejects claims 1, 4-5, 7-9, 11-16, and 29-30 under 35 U.S.C. 112, 1st paragraph, as allegedly failing to comply with the written description requirement.

Action at pages 3-4. Specifically, the Examiner raises new matter rejections on the grounds that support allegedly is lacking for the following claim elements:

- "wherein the group Y meningococcal polysaccharide fragment ... is completely N-acetylated and wherein the carrier protein is covalently coupled to the group Y meningococcal polysaccharide fragment at the de-O-acetylation sites"; and
- "wherein said polysaccharide is selected from the group consisting of an O-acetyl negative group Y and a fragment of an O-acetyl positive group Y meningococcal polysaccharide, wherein the fragment of an O-acetyl positive group Y meningococcal [polysaccharide] ... is completely N-acetylated, wherein the carrier protein is covalently coupled to the polysaccharide at the de-O-acetylation sites."

As an initial matter, Applicants note that claim 30 is canceled herein, mooting the rejection respect to this claim. Applicants further respectfully point out that "[m]ere rephrasing of a passage does not constitute new matter." MPEP 2163.07. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). Moreover, the objected-to elements contain only two aspects introduced by way of amendment in Applicants' prior response, namely:

- a "**completely N-acetylated**" O-acetyl positive group Y meningococcal polysaccharide fragment; and

- covalent coupling of the carrier protein to the group Y meningococcal polysaccharide fragment "**at the de-O-acetylation sites**".

Support for each of these aspects indeed can be found in the original specification. Moreover, the phrase "at the de-O-acetylation sites" has been further amended to specify that carrier protein is covalently coupled to the polysaccharide "through cleaved sialic acid exocyclic side chains of the polysaccharide fragments", as clearly taught in the specification.

"**Complete N-acetylation**" of an O-acetyl positive group Y meningococcal polysaccharide fragment finds support, e.g., at paragraph [0039], where it is stated:

> "The de-O-acetylated polysaccharide, regardless of whether or not it has been subjected to acid hydrolysis, may optionally undergo re-N-acetylation. This step ensures that *all free primary amines* that may have been generated during the base hydrolysis *are re-N-acetylated.*" (Emphasis added).

As "*all free primary amines ... are re-N-acetylated*," it clearly follows that there is "**complete N-acetylation**" of the polysaccharide. See also, paragraph [0092]-[0093], discussing re-N-acetylation of the polysaccharide fragment, whether originally O-acetyl positive or O-acetyl negative. Further, as noted above, support may be found at paragraph [0093] that reports the percent of O-acetylation relative to the N-acetyl groups of the sialic acid groups per repeat unit, stating that there are 0.6 M of O-acetyl positive per repeating unit "(or 60% relative to the N-acetyl group of sialic acid) equally distributed between the C7 and C9 position of their scialic acids." This is an example of the use of a polysaccharide that is not completely O-acetyl negative but completely N-acetyl positive. The equivalence of the 0.6 M per repeat unit with the 60% of scialic acids implies that each repeat unit has a corresponding N-acetyl group, further supporting

the element that the polysaccharides are completely N-acetylated. Accordingly, there is no issue of new matter with respect to the claim element regarding a "**completely N-acetylated**" O-acetyl positive group Y meningococcal polysaccharide fragment.

The same holds true with respect to the aspect concerning covalent coupling of the carrier protein to the group Y meningococcal polysaccharide fragment "**at the de-O-acetylation sites**", and more specifically "through cleaved sialic acid exocyclic side chains of the polysaccharide fragments." As noted in Applicants' previous response, support for the amendment can be found, e.g., at paragraphs [0066]-[0068], which describe coupling carrier protein to the polysaccharide by reductive amination at activated carbonyl groups formed at de-O-acetylation sites. Specifically, paragraph [0067] provides that:

> "Selective reductive coupling agents are though (*sic*) to act as a mild selective reducing agent of the Schiff base intermediate that is *formed between the carbonyl groups of the polysaccharide and the amino groups of the carrier protein*." (Emphasis added).

Furthermore, as the specification teaches that any free primary amines, resulting from de-N-acetylation, can be re-N-acetylated (see paragraph [0039], above), it clearly follows that in such embodiments no de-N-acetylation sites remain available for protein conjugation, so that carrier protein is necessarily covalently coupled to the polysaccharide "**at the de-O-acetylation sites**." The specification further states that the de-O-acetylated polysaccharide can be activated by oxidation to introduce aldehyde groups into the exocyclic side chain of the sialic acids, which are then used to couple carrier protein to provide a conjugated product containing de-O-acetylated Y *Neisseria* meningococcal polysaccharide fragment conjugated to a suitable carrier protein. See paragraphs [0049] to [0054], which provide support for the element of the claim discussed by the Examiner.

The specification further indicates that, in some embodiments, the aldehyde groups preferably can be introduced at C-8, and can be introduced through the cleaved sialic acid exocyclic side chains of the polysaccharide fragments (see paragraph [0053] and Figure 1). Thus the specification provides clear support for the amended element, specifying that carrier protein is covalently coupled to the polysaccharide "through cleaved sialic acid exocyclic side chains of the polysaccharide fragments."

Accordingly, Applicants respectfully request reconsideration and withdrawal of the new matter rejections directed at these aspects of the subject claims.

New Rejections under35 U.S.C. 112, 2nd paragraph

Claims 1, 4-5, 7-9, 11-16, and 29-30 are rejected under 35 U.S.C. 112, 2nd paragraph, as allegedly being indefinite. Action at page 4. Specifically, the Examiner rejects claims 1 and 30, and dependent claims 4, 5, 7-9, 11-16, and 29 as indefinite for reciting the limitation "less than about". Id. Without acquiescence, Applicants have canceled claim 30 and amended independent claim 1 to delete reference to the term "about." Accordingly, the rejection is rendered moot.

Claim 29 further is rejected as indefinite for not reciting "the." Id. Again without acquiescence, Applicants have amended this claim to recite "The," rending moot the indefiniteness rejection of this claim.

For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejections directed at the subject claims.

Rejections under 35 U.S.C. 103(a)

The Office rejects claims 1, 4-5, 7-9, 11-16, and 29-30 under 35 U.S.C. 103(a) as allegedly obvious in view of Costantino WO 03/007985 and Porro U.S. 2006/0165730, and further in view of Michon et al. US 2004/0213804. Action at pages 4-9. The Office alleges that Costantino teaches a polysaccharide fragment from O-acetyl positive group Y of *N. meningitis*, having a MW less than about 150 kDa, at least 80% O-deacetylation and complete N-acetylation, where the polysaccharide fragment is conjugated to a carrier protein, but acknowledges that Costantino does not teach that the carrier protein is covalently coupled to the polysaccharide at the de-O-acetylation sites. Action at pages 6-7. The Office apparently points to Porro as teaching coupling via such sites; and apparently to Michon as teaching complete N-acetylation of an immunogenic polysaccharide-protein conjugate, where the protein is directly coupled through beta-position sites of propionate moieties of the N-propionated poly- or oligosaccharide. Action at pages 7-8.

Accordingly, the Examiner continues, it would have been *prima facie* obvious to modify Costantino's polysaccharide by Porro's de-O-acetylation to covalently couple carrier protein at the de-O-acetylation sites; and further by Michon's complete N-acetylation and conjugation. Action at page 8. For motivation, the Examiner references the avoidance of sterical hindrance of interacting a protein and a polysaccharide, as discussed in Porro, and not altering the epitope of the polysaccharide conjugate, as discussed in Michon. Id.

As an initial matter, Applicants note the claim 30 is canceled herein, without any acquiescence. With respect to the remaining claims under this rejection, Applicants

respectfully traverse because none of the cited references in fact teach a completely N-acetylated polysaccharide fragment that has been subjected to base hydrolysis and, moreover, none provide motivation to completely N-acetylate a polysaccharide fragment that is covalently coupled to carrier protein through cleaved sialic acid exocyclic side chains of the polysaccharide fragments, as required by the now-pending claims.

1. No reference teaches a completely N-acetylated polysaccharide

The Office allegedly finds completely N-acetylated polysacchrides in both Costantino and Michon. Action at pages 6 and 8. However, neither of these references in fact teaches complete N-acetylation of a polysaccharide fragment following de-O-acetylation by base hydrolysis, as required by the subject claims.

Michon teaches a method of preparing an immunogenic polysaccharide-protein conjugate by removing N-acetyl groups from the polysaccharide and replacing them with N-acryloyl groups, which in turn are coupled to protein. See Michon, paragraph [0021]. Michon, however, does not teach de-O-acetylation, nor de-O-acetylation by base hydrolysis. Moreover, as noted in previous responses, Michon fails to teach complete N-acetylation as Michon explicitly states that *only a portion* of the de-N-acetylated groups are converted into N-acryloyl groups for coupling to protein:

> "[a] percentage of the N-acetyl groups removed by hydrolysis from the polysaccharide are replaced by N-acryloyl groups, which in turn, are directly coupled to protein to form the conjugate of the present invention. Michon, paragraph [0022].

As some de-N-acetylated groups remain, it is evident that the polysaccharides of Michon are not "completely N-acetylated", even less so completely N-acetylaed following de-O-acetylation by base hydrolysis, as required by the currently-amended claims.

Furthermore, since N-acetyl groups are substituted by N-acryloyl groups, Michon teaches away from Applicants' invention.

Costantino cannot correct this deficiency, and neither can Porro. Costantino and Porro both teach hydrolysis of polysaccharides that are eventually coupled to carrier protein via reductive amination, but neither suggests or hints at re-N-acetylation following base hydrolysis. Base hydrolysis of the polysaccharide, however, can generate free primary amines, which remain as de-N-acetylation sites if not re-N-acetylated. See paragraph 0039 of the instant specification.

Porro teaches de-O-acetylation by hydrolysis, followed by activation at the de-O-acetylated sites, which are then coupled using a spacer to activated carrier protein via reductive amination. See paragraphs [0025]-[0045]. Some embodiments specify hydrolysis using a base, e.g., hydrolysis with anhydrous hydrazine. See paragraph [0027]. Nonetheless, Porro fails to recognize, much less addresses, the problem of de-N-acetylation to generate free primary amines following such base hydrolysis, as taught in the instant specification. Accordingly, Porro fails to teach or suggest re-N-acetylation of the resulting free primary amines following base hydrolysis, necessarily leading to conjugates in such embodiments where the polysaccharide fragment is not "completely N-acetylated", as required by the now-pending claims.

Costantino also teaches hydrolysis of the polysaccharide and eventual conjugation to a carrier protein via reductive amination. See pages 15-18. Nonetheless, Costantino specifies acid, rather than base, hydrolysis. See page 15, under Hydrolysis. Accordingly, Costantino also fails to disclose a completely N-acetylated polysaccharide fragment that

has been de-O-acetylated by base hydrolysis, as required by the currently-amended claims.

As neither Costantino, nor Porro, nor Michon can provide the required element of complete N-acetylation of a polysaccharide fragment that has been de-O-acetylated by base hydrolysis, there can be no *prima facie* case of obviousness based on the cited references.

For at least this reason, Applicants respectfully request reconsideration and withdrawal of the rejections directed at claims 1, 4-5, 7-9, 11-16, and 29, as currently-amended.

2. There is no motivation to re-N-acetylate the polysaccharide

Applicants respectfully submit that the cited references also fail to provide any motivation to re-N-acetylate a polysaccharide that has been de-O-acetylated by base hydrolysis and that is covalently coupled to carrier protein through cleaved sialic acid exocyclic side chains of the polysaccharide fragments, as required by the currently-amended claims, rather than at de-N-acetylation sites, as in Michon. As noted above, Michon teaches converting polysaccharide N-acetyl groups into N-acryloyl groups, which in turn are coupled to protein to form conjugates. See Michon, paragraph [0021]. Thus in Michon, the carrier protein is coupled at de-N-acetylation sites rather than de-O-acetylation sites, and N-acryloylation is carried out to form the polysaccharide-protein conjugates, rather than relying on reductive amination.

In contrast, Porro and Costantino teach hydrolysis of the polysaccharide and conjugation to carrier protein via reductive amination. Unlike the instant specification, however, neither reference recognizes, much less addresses, the problem of de-N-

acetylation and generation of free primary amines during base hydrolysis. Without any such recognition of this potential issue, there would be no reason or motivation to carry out re-N-acetylation to arrive at the completely N-acetylated polysaccharide fragments of the instant claims.

Michon does nothing to provide the missing motivation. Michon's N-acryloylation is carried out in a completely different context from the conjugation reactions of Porro and Costantino. Rather than de-O-acetylation and reductive amination, Michon intentionally de-N-acetylates the polysaccharide to form N-acryloylates to then couples the carrier protein at de-N-acetylation sites using the N-acryloyl residues. Applicants respectfully submit that one of skill in the art thus would have no motivation to modify the polysaccharides of Costantino or Porro by the N-acryloylation taught in Michon, as Costantino and Porro use very different coupling reactions to form distinctly different conjugate products. Moreover, the result of using the method taught by Michon of substituting N-acryloyl for N-acetyl groups teaches away from Applicants' invention which relates to complete N-acetylation.

While the Examiner alleges general motivation for modifying Costantino's polysaccharide fragments, involving avoiding steric hindrance, discussed in Porro, and maintaining the epitope, discussed in Michon, the Examiner in no way explains how one would come to the conclusion to completely re-N-acetylate a polysaccharide used in one type of conjugation reaction based on a very different coupling reaction that forms a distinctly different conjugate product. Without any motivation to modify Costantino's or Porro's polysaccharides with Michon's N-acryloylation, Applicants respectfully submit that there can be no *prima facie* case of obviousness in view of the cited references.

In sum, Applicants note that none of the cited references, alone or in combination, recognize nor address the importance of complete re-N-acetylation following de-O-acetylation by base hydrolysis of meningococcal Y polysaccharides, in the context of preparing immunogenic conjugates and as taught by the instant inventors. The art failed to recognize that any remaining free primary amines could compromise the integrity of the immunogenic conjugate, e.g., by zwitter ion formation or oxidative cleavage of the polysaccharide component. Indeed, current studies indicate that the group Y meningococcal polysaccharide epitope is a relatively large structure, comprised of 5 to 6 repeating sugar units. Moore et al. (2007), *Clinical and Vaccine Immunology,* 14(10): 1311-1317. As breakage at any remaining de-N-acetylated sites would destroy this large epitope structure, complete N-acetylation is particularly important for retaining antigenicity in group Y meningococcal vaccines.

For at least one or more of the above reasons, Applicants respectfully request re-consideration and withdrawal of the non-obviousness rejections directed at claims 1, 4-5, 7-9, 11-16, and 29, as currently-amended.

Lastly, the Examiner notes that the limitations of claims 1 and 16 regarding "use as a vaccine against *N. meningitidis* infection" and "wherein the vaccine is adapted for injection" are considered statements of "intended use" and given no weight regarding the patentability of the conjugates. Applicants note in reply, however, that these limitations are not replied upon in showing nonobviousness of these claims, as outlined above.

CONCLUSION

In view of the foregoing remarks and amendments, Applicants respectfully submit that claims 1, 4-5, 7-9, 11-16, and 29, as currently amended, are in condition for allowance and respectfully request timely notification of same. In the event that the Examiner believes that issues exist that can be resolved by telephone conference, or that any formalities can be corrected by an Examiner's Amendment, a telephone call to the undersigned at (212) 827-4318 is respectfully requested.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-3732, Order No. 00518-105087. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No. 00518-105087.

Respectfully submitted,
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